

REMARKS

Applicants have amended claim 1 to recite "consisting" and to clarify that the an LFA-1 antibody is used in combination 40-O-(2-hydroxyethyl)-rapamycin. Support for these amendments may be found in the specification at page 14, second paragraph, where administration of anti-LFA-1 mAb and 40-O-(2-hydroxyethyl)-rapamycin occurs in the absence of anti-CD154 mAb.

Because the cited reference WO01/95928 at least does not disclose a method consisting of administration of the combination of 40-O-(2-hydroxyethyl)-rapamycin and an anti-LFA-1, the instant method claims are not anticipated by this reference. For this reason, Applicants respectfully request withdrawal of the rejection of pending claims 2 and 13 as anticipated under 35 U.S.C. §102(e) by WO01/95928.

Regarding the 35 U.S.C. §103 rejection of claims 2 and 13 as being unpatentable over US 6,653,282 or WO95/34320 in view of US 6,486,209 and US 200201524900, Applicants respectfully submit that this combination of references does not render obvious the instantly pending claims.

Graham v. John Deere Co. of Kansas City, 383 U. S. 1, 17-18 (1966), establishes an objective analysis for applying §103 to a question of obviousness: "the scope and content of the prior art are . . . determined; differences between the prior art and the claims at issue are . . . ascertained; and the level of ordinary skill in the pertinent art resolved." The United States Patent and Trademark Office bears the burden of establishing a *prima facie* case of obviousness based on the results of the factual inquiries under *Graham*. The *prima facie* case generally requires three showings: 1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; 2) a reasonable expectation of success; and 3) that the prior art reference or combination of references teaches or suggests all the claim limitations. MPEP §2143.

Applicants do not concede that the combination of references cited by the Office is appropriate for reasons of record. Moreover, even if such a combination were appropriate, said combination would not contain all elements of Applicants pending claims, which showing is required to establish *prima facie* obviousness under *Graham*. As admitted by the Office on page

4 of the instant Office Action, the primary references cited in the obviousness rejection, i.e., US 6,653,282 and WO95/34320, both disclose a combination therapy that requires an LFA-1 inhibitor and a co-stimulatory inhibitor. As amended, Applicants claims focus on a method for inducing hematopoietic chimerism in a recipient of cells, tissue or organ transplant from a donor consisting of additionally administering to the recipient bone marrow cells or other precursor cells from the donor; and an LFA-1 antibody in combination with 40-O-(2-hydroxyethyl)-rapamycin. Applicants claims therefore do not recite a combination therapy that requires an LFA-1 inhibitor and a co-stimulatory inhibitor. This deficiency in the primary references is not supplied by the secondary references, which also do not disclose or suggest that an LFA-1 inhibitor may be used in combination with 40-O-(2-hydroxyethyl)-rapamycin for inducing hematopoietic chimerism.

The failure of an asserted combination to teach or suggest each and every feature of a claim remains fatal to an obviousness rejection under 35 U.S.C. § 103, despite any recent revision to the MPEP. Section 2143.03 of the MPEP requires the "consideration" of every claim feature in an obviousness determination. To render the instant independent claims unpatentable, however, the Office must do more than merely "consider" each and every feature for this claim. Instead, the asserted combination of references must also teach or suggest each and every claim feature. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (emphasis added) (to establish *prima facie* obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art). Indeed, as the Board of Patent Appeal and Interferences has recently confirmed that a proper obviousness determination requires that the Office make "a searching comparison of the claimed invention - *including all its limitations* - with the teaching of the prior art." *See In re Wada and Murphy*, Appeal 2007-3733, *citing In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). Further, the necessary presence of all claim features is axiomatic, since the Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including ascertaining the differences between the claimed invention and the prior art. *Graham*, 383 U.S. 1 (1966). Indeed, Applicants submit that this is why Section 904 of the MPEP instructs examiners to conduct an art search that covers "the invention as *described and claimed*." (emphasis added). Lastly, Applicant respectfully directs attention to MPEP § 2143, the instructions of which buttress the conclusion that obviousness requires at least a suggestion of all of the features of a claim, since the Supreme Court in *KSR Int'l v. Teleflex Inc.* stated that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

In sum, it remains well-settled law that obviousness requires at least a suggestion of all of the features in a claim. See *In re Wada and Murphy*, citing *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (stating “obviousness requires a suggestion of all limitations in a claim.”) and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). In the instant situation, the combination of references does not suggest all the features of Applicants’ pending claims. For at least this reason, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

A proper *prima facie* case of obviousness must also establish that there is a reasonable expectation of success at arriving at Applicants’ invention upon combining the cited references *Graham*; *In re O’Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). In the instant situation, there is no reasonable expectation that, given publications suggesting the requirement of an LFA-1 modulator and a co-stimulatory inhibitor to modulate certain immune responses, modulation may be had without using a co-stimulatory inhibitor. This lack of reasonable expectation of success is fatal to any obviousness case under *Graham*. For at least this reason, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Applicants also submit that even if a *prima facie* case of obviousness were established, Applicants’ disclosure of surprising and unexpected results obtained for the instantly claimed methods would rebut such a showing. The current relevant inquiry into the question of non-obviousness is “. . . [w]hether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR Int’l Co. v. Teleflex Inc.*, 127 S.Ct 1727, 1731, 82 USPQ2d 1385, 1396 (2007). The Supreme Court has held that secondary considerations such as unexpected results and important advantages are relevant as indicia of non-obviousness. *Graham*, 383 U.S. at 17-18. Evidence of such secondary considerations, where present, must be considered in a determination of obviousness. *Stratoflex, Inc. v. Aeroquip Corporation*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983). The Office is also required to consider what the prior art as a whole teaches. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) (stating that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention). The MPEP specifically requires the Office to “consider[] both the invention and the prior art references as a whole” and warns of distilling an invention down to a “gist” or “thrust”, as such distillation disregards the “as a whole” requirement for an obviousness analysis. See *W.L. Gore*, 721 F.2d 1540 (Fed. Cir. 1983); MPEP § 2141.02. Applicants respectfully submit that the claimed subject matter provides advantages which could not have been predicted from the disclosures of the cited references, either alone or in combination, and that the art as a whole taught away from what Applicants now claim.

On page 14 of the instant application, Applicants discuss the results for an experiment in which chimerism in the absence of anti-CD154 antibody is observed when anti-LFA-1 mAb is combined with 40-O-(2-hydroxyethyl)-rapamycin. The application states that “[o]verall levels of chimerism for each cell type are also obtained when applying any of these three synergistic principles, i.e., antiCD154 + 40-(2-hydroxyethyl)-rapamycin (Fig. 1), anti LFA-1 + anti CD154 (Fig. 2 and Fig. 3) and LFA-1+40-(2-hydroxyethyl)-rapamycin (Fig. 3).”¹ As admitted by the Office on page 4 of the instant Office Action, the primary references cited in the obviousness rejection, i.e., US 6,653,282 or WO95/34320, both disclose a combination therapy that requires an LFA-1 inhibitor and a co-stimulatory inhibitor. Moreover, WO01/95928 provides that one would require interference with at least three different cell surface molecules with their different ligands, i.e., CD28/B7/CTLA4, CD40/CD154 and LFA-1, in order to regulate cell-mediated immune responses (e.g., allograft transplant rejection). In contrast to what was known in the art at the time of filing the instant application, Applicants methods achieve synergy in inducing hematopoietic chimerism in a recipient of cells, tissue or organ transplant from a donor using an LFA-1 antibody in combination with 40-O-(2-hydroxyethyl)-rapamycin. Accordingly, Applicants assert that even if, *arguendo*, the Office could maintain that the combination of references renders obvious Applicants' instant claims, such surprising and/or unexpected results rebut a *prima facie* case of obviousness. See MPEP §2144.09 (*citing In re Papesch*, 315 F.2d 381 (CCPA 1963)). Furthermore, there is no reasonable expectation from the cited references, alone or in combination, of similar properties, which is further demonstrated by Applicants' surprising results. See MPEP §2144.09.

Based on the evidence as a whole, the combination of references does not support a finding of *prima facie* obvious. See MPEP § 2144.08; *In re Bell*, 991 F.2d 781,784 (Fed. Cir. 1993); *In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990)). The Office has not provided a combination of references that provides all the elements of Applicants pending claims, nor has the Office shown a reasonable expectation of success at achieving Applicants' claimed subject matter. In the present application, the results of the factual inquiries under Graham do not support that the pending claims are *prima facie* obvious under 35 U.S.C. §103(a). Moreover, Applicants respectfully submit that any *prima facie* case has been successfully rebutted and overcome. Accordingly, Applicants respectfully request withdrawal of the obviousness-based rejection of the pending claims.

¹ The figures appear to have inadvertently not been filed with the International Application or this National Phase entry. However, such figures, which merely reflect the discussion in the specification at page 14, may be found in the original GB priority application (GB 0217777.2), which was transmitted by the IB to the USPTO. The Office is encouraged to look at such figures if need be.

CONCLUSION

In light of the above amendments, observations and remarks, Applicants respectfully submit that the presently claimed invention satisfies 35 U.S.C. §112, and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims in this application is earnestly solicited.

Applicants' undersigned attorney may be reached in our New Jersey office by telephone at (862) 778-9308. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,



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